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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,701	10/02/2003	Victor V. Levenson	NWESTERN-08390	9778

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EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/677,701	LEVENSON ET AL.	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 21-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 21-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed May 3, 2006. Currently, claims 1-15, 21-24 are pending.

Election/Restrictions

2. In view of the amendments to the claims to require a combination of all 8 genes in Claim 3, the restriction requirement to a particular combination of genes has been withdrawn.

Priority

3. This application claims priority to provisional 60/415,628, filed October 2, 2002.

Drawings

4. The drawings are acceptable.

3Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-2, 21, 23-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Yan et al. (Clinical Cancer Research, Vol. 6, pages 1432-1438, April 2000).

Yan et al. teaches CpG Island arrays for deciphering epigenetic signatures of breast cancer. Yan teaches an array based method for differential methylation hybridization (DMH) which allows for genome-wide screening of CpG island hypermethlation. Yan studied 28 paired primary breast tumor and normal samples to determine whether patterns of specific epigenetic alterations correlate with pathological parameters in patients analyzed (abstract). Yan teaches that close to 9% of the 1104 CpG island tags exhibited extensive hypermethylation in the majority of breast tumors relative to their normal controls, whereas others had no detectable changes (abstract)(limitations of Claim 23). Yan specifically teaches obtaining patient samples from female patients undergoing mastectomies to isolate high molecular weight DNA (limitations of Claim 21, 24). Yan further teaches genomic DNA was digested with MseI which is methylation sensitive and followed by amplification (page 1433, col.1)(limitations of Claim 2). Yan teaches performing array hybridization on nylon membranes (page 1433, col. 2). Yan teaches normal and tumor amplicons were analyzed. As seen in Figure 1, the results of DMH are illustrated. Yan teaches hypermethylation of numerous nucleic acids. Thus, Yan teaches detecting DNA methylation by comparing tumor and normal paired samples to a control.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 3-13, 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yan et al. (Clinical Cancer Research, Vol. 6, pages 1432-1438, April 2000) in view of Ferguson et al. (Current Genomics, Vol. 1, pages 41-58, 2000) and Herman et al. (Cancer Research, Vol. 56, pages 722-727, February 1996) and Bovenzi et al (Anti-Cancer Drugs, Vol. 10, pages 471-476, 1999) and Du et al. (Cancer Research, Vol. 61, pages 8094-8099, November 2001) and Paz et al (Cancer Research, Vol. 62, pages 4519-4524, August 2002) and Worm et al. (J. of Biological Chemistry, Vol. 276, No. 43, pages 39990-40000, August 2001).

Yan et al. teaches Cpg Island arrays for deciphering epigenetic signatures of breast cancer. Yan teaches an array based method for differential methylation hybridization (DMH) which allows for genome-wide screening of Cpg island

hypermethlation. Yan studied 28 paired primary breast tumor and normal samples to determine whether patterns of specific epigenetic alterations correlate with pathological parameters in patients analyzed (abstract). Yan teaches that close to 9% of the 1104 Cpg island tags exhibited extensive hypermethylation in the majority of breast tumors relative to their normal controls, whereas others had no detectable changes (abstract)(limitations of Claim 23). Yan specifically teaches obtaining patient samples from female patients undergoing mastectomies to isolate high molecular weight DNA (limitations of Claim 21, 24). Yan further teaches genomic DNA was digested with MseI which is methylation sensitive and followed by amplification (page 1433, col.1)(limitations of Claim 2). Yan teaches performing array hybridization on nylon membranes (page 1433, col. 2). Yan teaches normal and tumor amplicons were analyzed. As seen in Figure 1, the results of DMH are illustrated. Yan teaches hypermethylation of numerous nucleic acids.

Yan does not specifically teach analyzing each of the recited genes from the panel of genes claimed.

However, Ferguson teaches DNA methylation in Breast Cancer by analyzing a panel of genes. Ferguson teaches numerous genes methylated in human breast cancer include MDGI, PR, S100A2, E-cadherin, GST, BRAC1 and calcitonin. Ferguson acknowledges the use of DNA array based technique called differential methylation hybridization to screen for hypermethylated CpG islands in a panel of cells (page 44, col. 2).

Herman teaches hypermethylation of p15 is inactivated in association with promoter region hypermethylation in breast cancer (abstract).

Bovenzi et al. teaches retinoic acid receptor B (RARB) is a putative tumor suppressor gene which is methylated in the promoter region of RARB in several breast tumors. Bovenzi further teaches other cancer-related genes have been reported to be silenced by DNA methylation including p16, E-cadherin and estrogen receptor. Bovenzi teaches that 5-Aza-CdR is an interesting agent to investigate in patients with breast cancer resistant to conventional chemotherapy (limitations of Claim 5).

Du teaches hypermethylation in human cancers of the RIZ1 tumor suppressor gene. Du teaches the loss of RIZ1 mRNA in human cancers is associated with DNA methylation of its promoter CpG island. Du teaches methylation of the RIZ1 promoter strongly correlated with mRNA expression in breast cancer. Du teaches 11 of 25 (44%) of breast cancer specimens showed methylation (abstract).

Paz et al. teaches DNA methylation in normal tissues and human primary tumors. Paz specifically teaches analyzing the epigenetic features of the 5-methyl-cytosine content in the genome of the tumors and their normal counterparts and the presence of CpG island hypermethylation of tumor suppressor genes including DAPK, GSTP1, BRCA1 and RARB2 (abstract). Paz teaches a profile of CpG island hypermethylation (see page 4521, col. 2).

Worm teaches the MDR1 promoter CpG island is demethylated in 5-axa-2'deoxycytidine associated human breast cancer.

Therefore it would have been prima facie obvious to the ordinary artisan at the time the invention was made to have modified the profiling method of Yan to include additional known methylated genes of Ferguson, Herman, Bovenzi, Du, Paz and Worm. The ordinary artisan would have been motivated to have included any number of CpG islands on the array for detecting and deciphering epigenetic signatures of breast cancer. Yan teaches that the arrays may be used for a population-based DMH study and demonstrates the need develop a database for examining large-scale methylation data and for associating specific epigenetic signatures with clinical parameters in breast cancer. The array panel of Yan contains 1104 CpG island tags for analysis. The ordinary artisan would have been motivated to have included each of DAPK, GSTP, p15, MDR1, PR, Calcitonin, RIZ, RARB genes on the array for analysis.

8. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yan et al. (Clinical Cancer Research, Vol. 6, pages 1432-1438, April 2000) and Ferguson et al. (Current Genomics, Vol. 1, pages 41-58, 2000) and Herman et al. (Cancer Research, Vol. 56, pages 722-727, February 1996) and Bovenzi et al (Anti-Cancer Drugs, Vol. 10, pages 471-476, 1999) and Du et al. (Cancer Research, Vol. 61, pages 8094-8099, November 2001) and Paz et al (Cancer Research, Vol. 62, pages 4519-4524, August 2002) and Worm et al. (J. of Biological Chemistry, Vol. 276, No. 43, pages 39990-40000, August 2001) and further in view of Huang (US Pat. 6,605,432, August 12, 2003).

Neither Yan, Ferguson, Herman, Bovenzi, Du, Paz nor Worm specifically teach using the Hin6I methylation sentivie enzyme for digesting.

However, Huang teaches anaylsis of high throughput methios for detecting DNA methylation. Huang teaches after amplification, methylation-sensitive sites of the amplified products are preferably identified by digestion with a methylation-sensitive restriction enzyme. Examples of such methylation-sensitive enzymes are BstU I, SmaI, SacII, EagI, MspI, HpaII, HhaI and BssHII which digest non-methylated CpG dinucleotide regions (limitations of Claim 14). Positive CpG dinucleotide nucleic acid fragments containing the methylation-sensitive sites are used for DMH analysis.

Therefore it would have been prima facie obvious to the skilled artisan at the time the invention was made to modify the method of Yan, Ferguson, Herman, Bovenzi, Du, Paz and Worm to digest with Hin6I, an equivalent methylation senstivite enzyme. Yan teaches digesting with BstUI. Huang teaches that BstUI and HhaI (also known as Hin6I) are methylation sensitive enzymes for digesting and analysis of methylation patterns.

Conclusion

9. No claims allowable over the art.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J. Goldberg

Jeanine Goldberg
Primary Examiner
July 16, 2006